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ROBERT DEBERARDINE
ABBOTT LABORATORIES
100 ABBOTT PARK ROAD
DEPT. 377/AP6A
ABBOTT PARK, IL 60064-6008

EXAMINER	
BERNHARDT, EMILY B	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 04/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/773,035	KOLASA ET AL.	
	Examiner	Art Unit	
	Emily Bernhardt	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-96* is/are pending in the application.

4a) Of the above claim(s) *12-17,21-31,39,49-52,55-62 and 70-96* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,10,18,19,32-38,40-48,53,54 and 63-69* is/are rejected.

7)☒ Claim(s) *8,11 and 20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/5/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-11,18-20,32-38,40-48,53,54,63-69, drawn to compounds,compositions and use to treating sexual dysfunction (SD) where Z=N, classified in class 544, subclasses such as 295,360,367; class 514 subclasses such as 252.14, 253.01,254.02.

II. Claims 1,2, 15-17,21-27,32-38,40,41,51,52,55-59 and 63-69, drawn to compounds,compositions and use to treating sexual dysfunction (SD) where Z=CH and 2nd R3 choice (piperidine), classified in class 546, subclasses such as 194; class 514 subclass 318,etc.

III. Claims 1,2,12-14,32-38,40,41,49-50 and 63-69, drawn to compounds,compositions and use to treating sexual dysfunction (SD) where Z=C (and double bond is present), classified in class 546, subclasses such as 257, 270.4,etc.; class 514 subclasses 334,342,etc.

IV. Claims 1,28-38,40,60-69, drawn to compounds,compositions and use to treating sexual dysfunction (SD) where R3 is 3rd ring (pyrrolidine), classified in classes such as 544, subclasses such as 336 and class 546,548; class 514 subclass 255.05,etc.

V. Claims 39 and 70, drawn to additional uses employing compounds of I-IV, classified in class 514, subclasses various.

VI. Claims 71,76-86,88-95, drawn to compounds,compositions and use to treating sexual dysfunction (SD) where R3= piperdines, classified in class 546, subclasses such as 231,232; class 514 subclass 331,etc.

VII. Claims 71-75,80-86, drawn to compounds,compositions and use to treating sexual dysfunction (SD) where R3=pyrrolidine, classified in class 548, subclass 569; class 514 subclass 428,429.

VIII. Claims 87,96, drawn to additional uses employing VI, classified in class 514, subclass 331.

IX. Claim 87, drawn to additional uses employing VII, classified in class 514, subclass 428,429.

X. Claims 88-95, drawn to use for treating SD and compositions employing formula III where R3= hydrogenated pyridine, classified in class 514, subclasses 428,429.

XI. Claim 96, drawn to additional uses for formula III where R3=hydrogenated pyridine, classified in class 514, subclass 331.

The inventions are distinct, each from the other because of the following reasons:

Compounds within groups I-IV and VI-VII relate to compounds of considerable structural dissimilarity in view of the varying cores based on R3 as well as nature of rings permitted thereon- heteroaryl vs aryl . Thus they are separately classified based at the very least on species recited in various claims. Each can support a patent as the compounds of each group are capable of being utilized alone not in combination with other members listed in the Markush group. Note the art applied below which is only pertinent to elected subject matter.

Inventions I-IV and V are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case more than one use exists for compounds claimed as evident by the many uses described as well as those described in the prior art applied below for elected compounds.

The same applies to Groups VI vs VIII and VII vs IX.

Groups X and XI have no corresponding compound group are directed to separate uses.

During a telephone conversation with Ms. Ferrari-Dileo on 3/9/06 a provisional election was made with right of traverse to prosecute the invention of I, claims 1-11,18-20,32-38, 40-48,53,54 and 63-69. Affirmation of this election must be made by applicant in replying to this Office action. Claims 12-17,21-31,39,49-52,55-62 and 70-96 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to

the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

The abstract of the disclosure is objected to because it does not convey actual structural makeup only variables are depicted which is not very informative. Correction is required. See MPEP § 608.01(b).

Claims 1-4,6,7,9,10,18,19,32-38,40-43,45-48,53,54,63-69 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Nature of prodrugs intended throughout the generic claims is not known since specification is silent as to what types are suitable . A prodrug is chosen based on some undesirable property present in the parent compound and once the type of improvement is identified there is testing to determine the prodrug's efficacy and ability to regenerate the parent compound. It is not the norm that one can predict with any degree of accuracy a particular prodrug form of an active compound will

be more soluble, more easily handled in formulations or more bioavailable without actual testing in vivo . Thus the design of prodrugs is far from trivial and is dependent on the undesirable properties of the active compound(s) which will vary from drug to drug. Thus in the absence of any guidelines (none is seen in the specification) as to what type of prodrugs are suitable for instant compounds and at which locations (COOH,OH,amino groups, acyl groups) it cannot be readily determined what is and what is not within the instant scope.

2. Claims 32-38 and 63-69 are independent claims as recited and thus need to be complete as written. Thus the scope of recited "formula" must be set forth in the claims or the claims made into dependent claims. Applicants should check these claims to avoid duplicates. Note that claim 64 is a duplicate of 33.

Claim5 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. There are at least 2 species not seen to be within the scope of claim 1 from which 5 ultimately depends. Note the "dioxime" species appearing on p.143- 4th and 7th species.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 5 is rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility. As the species pointed out above are outside the generic formula and are not elsewhere included within applicants' genus or have been particularly tested, they cannot be ascribed the uses taught for the generic embodiments.

Claims 1-4,6,7,9,10,18,19,32-38,40-48,53,54 and 63-69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The following reasons apply:

1. Applicants provide no reasonable assurance that any and all classes of known prodrugs will have the ability to regenerate **in vivo** to the instant compounds by one or more biological processes. It is not the norm that one can predict with any degree of accuracy a particular prodrug form of an active compound will be more soluble, more easily handled in formulations or more bioavailable without actual testing **in vivo** .Additionally, method claims include such moieties. Generally, prodrugs themselves are not considered to be

therapeutically active but only to provide the active compound **in vivo.** This rejection applies to all claims rejected listed above ;

2. Scope at R2 and R4 as heteroaryl is not adequately enabling. Specification's definition includes mono- and bicyclic rings having as many as 4 heteroatoms in any array. Compounds made represent the scope of claims 4 or 7 for R4 and the scope of claim 10 for R2. However, there is no reasonable assurance as to what other rings, ring systems will work as there is no actual test data for D4 receptor binding only a range is reported and thus no insight into structure-activity trends that need to be evaluated. Note In re Surrey 151 USPQ 724 regarding sufficiency of disclosure for a Markush group where as herein no examples of a diverse nature have been made much less tested showing the requisite activity needed to practice the invention. Also see MPEP 2164.03 for enablement requirements in cases directed to structure-sensitive arts such as the pharmaceutical art. Also note the criteria for enablement as set out in In re Wands cited in MPEP 2164.01(a),August 2000 edition, which includes factors such as:

1) Breadth of the claims- the claims cover compounds easily in the millions as pointed out above;

2) Level of unpredictability in the art- the invention is pharmaceutical in nature involving activity at the (D4) dopamine receptors. It is well established that

"the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be unpredictable. See In re Fisher 166 USPQ 18 The range in EC50 values is almost 1000-fold ;

3) Direction or guidance- compounds actually made and presumed tested represent a very small portion of a large heterogeneous scope ;

4) State of the prior art- The compounds are piperazine derivatives with an oxime or hydrazone group at one N terminus with varying heteroaryl rings at other nitrogen terminus as well as on carbon alpha to the oxime/hydrazone groups. While such compounds are known in the prior art as evident by the art applied below they are not directed to the same activity or uses;

5) Working examples- while test data has been described on p.131-132 no one compound has been identified as having been tested and thus no clear evaluation of which functional groups at various positions out of the many claimed might affect potency to a large or small degree.

This rejection is being applied towards claims 1-3,6,9,18,32-38,40-42,45,47 and 63-69;

3.) Other than treating male erectile dysfunction, the method claims which cover all forms of male and female sexually dysfunction are not adequately

enabled given the state of the current art in the dopamine area. References provided by applicants and cited in the specification on p.132 makes no such assertions.). At best they are directed to the treatment of MED and do not evidence that D4 agonists as a class can treat all sexual disorders in both male and female patients. Note especially refs. C7 and C8.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4 and 32 and 63 are rejected under 35 U.S.C. 102(b) as being anticpated by Buzas (GB'523 cited by applicants). Buzas describes a compound within the instant scope for use as an anti-inflammatory agent. See compound no.1 in Table II.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Buzas. While species in claim 5 are not anticipated by Buzas, there are several species which are obvious variants. These are the ethanone and propanone oximes that have the same R2 and R4 substituent as the anticipated species pointed out above but have methyl at R1 in place of allyl in Buzas. Note that Buzas teaches lower aliphatic groups which would alkyl as well as alkenyls as suitable choices at R1 and also teaches the alkylene chain can be 1 to 3 carbons which would include the ethanone and propanone analogs claimed herein. See 5^{th}-6^{th} species on p.141 and 7^{th}-8^{th} species on p.142 of claim 5. Thus it would have been obvious to one skilled in the art at the time the instant invention was made to modify the species in Buzas by altering the chain length corresponding to instant "L" as well as modifying the aliphatic group at instant R1 with the expectation that resulting compounds will also posses the uses taught by Buzas.

Claims 8,11 and 20 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The structural features required in these claims are not taught or suggested by the art of record or from a search in the pertinent art area.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Bernhardt whose telephone number is 571-272-0664.

If attempts to reach the examiner by telephone are unsuccessful, the acting supervisor for AU 1624, James O. Wilson can be reached at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

E Bernhardt

Emily Bernhardt
Primary Examiner
Art Unit 1624